ADDENDUM

Clinical Study Report CV131154

TITLE OF STUDY: Study of Blood Pressure Reduction with Irbesartan in Children and Adolescents

INVESTIGATORS: 55

STUDY CENTERS: 53 (32 in the US, 13 in Russia, 6 in Poland, and 2 in Hungary)

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 21-Jun-2002
Date last subject completed (LPLV) open-label Period D: 07-Jun-2004
Open-Label, Long-Term Extension Period D: Seven subjects were ongoing at the time of database lock (15-Mar-2004) for the original study report. Safety Data for these 7 subjects are presented in this addendum.

CLINICAL PHASE: III

INTRODUCTION: This multicenter, randomized, double-blind, dose ranging study evaluated the safety and effectiveness of a range of irbesartan doses in the treatment of children (6 years - Tanner stage < 3) and adolescents (Tanner stage ≥ 3 - < 17 years) with hypertension or high-normal BP.

The study consisted of 4 periods. This addendum presents information on the last 7 subjects to complete Period D, the last of the 4 study periods, which was an open-label extension.

Study design, dose regimens, protocol/statistical methodology, efficacy, and safety results, were presented in the original clinical study report (CSR) dated 14-Jun-04. At the
Baseline Demographic and Disease Characteristics

All 7 subjects (5 males/2 females) were black. Ages ranged from 12 - 16 years, all with Tanner stage $\geq 3$. All subjects were $\geq 60$ kg. Five subjects were hypertensive; 2 subjects were high normal (Appendix ADDN 13.3).

RESULTS:

Efficacy

Measurements of BP and HR for the 7 subjects were consistent with their earlier Period D values (Appendix ADDN 13.3).

Safety

Adverse Events:

No deaths were reported for the 7 subjects. One subject (CV131154-1-19) experienced a serious adverse event (SAE; Appendix ADDN 13.4.3 and Appendix ADDN 5.1D) of diabetic ketoacidosis (see Laboratory Evaluations below). The SAE was considered unrelated to study drug and no action with respect to study drug was taken.

Adverse events (AEs) were reported for 3 subjects (Appendix ADDN 12.0) post database lock for the original report. Subject CV131154-1-21 experienced myalgia, nausea, and headache. Subject CV131154-3-9 experienced allergic rhinitis and subject CV131154-11-18 experienced bronchitis and sinusitis. Nausea and headache were considered possibly related to study drug; all other AEs were considered unrelated. Headache was severe; all other AEs were mild to moderate. Mild nausea was the only AE that required a dose reduction.

None of the 7 subjects discontinued from the study because of an AE or any other reason.

Appendix ADDN 12.0 includes updated information for subject CV131154-1-22 who experienced hematuria and upper respiratory tract infection prior to 15-Mar-2004 datalock for the original study report.

Laboratory Evaluations:

A marked laboratory abnormality (MA) was reported for 1 subject (CV131154-1-19; Appendix ADDN 13.4.5.1). This subject had a newly reported serum glucose of 768 mg/dL at the end of study visit on 15-Mar-2004 (Appendix ADDN 13.4.5). The subject experienced an SAE of diabetic ketoacidosis on 01-Mar-2004 that resolved on 05-Mar-2004 (Appendix ADDN 13.4.3). The investigator considered the elevated serum glucose of 768 mg/dL to be clinically significant and related to the diabetic ketoacidosis. Other
laboratory tests relevant to the SAE and performed on 15-Mar-2004 included HbA1c = 13.6% (baseline = 2 - 6%), urine ketones = 160 mg/dL (baseline = 0), and urine glucose ≥ 2000 mg/dL (baseline = 0). The subject had previously experienced diabetic ketoacidosis on study drug (SAE in the double-blind Period C on 11-Sep-2003 while taking 4.5 mg irbesartan) and elevated glucose (452 mg/dL) was reported on 12-Sep-2003. These events were reported in Appendix 13.4.3 and Appendix 13.4.5.1 of the original Clinical Study Report for study CV131154 - 14-Jun-2004.

CONCLUSIONS:

- Safety data for the last 7 subjects (aged 12 to 16 years) to complete the study are consistent with the overall conclusions of the original Clinical Study Report CV131154. There were no remarkable findings.
- Irbesartan is safe and generally well tolerated in adolescents with hypertension or high normal blood pressure.

DATE OF REPORT: 09-Dec-2004